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# Antioxidant Activity of *Lactococcus lactis* and Curcumin Inhibits Lifespan Shorten and Oxidative Stress in *Drosophila melanogaster*

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**KEYWORDS**

Oxidative stress; Alzheimer disease; life-span; flight ability; *Lactococcus lactis*.

**A B S T R A C T**

Oxidative stress has been strongly correlated with Alzheimer disease (AD) pathogenesis and the formation of intracellular Aβ42has been reported in AD *Drosophila* model. In this study, the effect of curcumin and *Lactococcus lactis* was studied on lifespan, flight ability and oxidative stress in the AD *Drosophila* model flies and oxidative stress and protein carbonyl content were investigated in the fly brains. The progeny (AD flies) expressing human Aβ42was exposed to 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LAL in the diet for 7 days. The result showed that the treatment of flies to curcumin and LAL induced a dose dependent significant delay of life-span, reduction in the oxidative stress and increase in the flight ability of AD *Drosophila* model. As a result, we concluded that curcumin and LAL can be potent in reducing AD symptoms.

## Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease and the most common cause of dementia. The pathogenesis of AD is yet entirely clear and despite the increasing knowledge regarding the mechanism, no effective disease-modifying therapy is yet available. Recently, many reports have shown to play a pivotal role in the synaptic damage, impairment of homeostasis, inflammation as well as toxicity in relation to AD etiology. Membranes can also be injury by the reactive oxygen species (ROS) that are produced by Aβ aggregates in the presence of metals such as copper, zinc or iron (Bush, 2003). Subsequent pathophysiological processes include mitochondrial damage (Abramov and Canevari, 2004), phosphorylated-Tau with consequent axonal transport damage and the trigger of cell death (Kienlen-Campard P and Miolet). However, until recently it has been impossible to take a global view to ask which biological processes are essential for the induction of the disease and which are downstream consequences of neurocytotoxicity (Cao and Song, 2008).

Knowing which biological processes are directly involved in initiating AD will allow us to key on those upstream targets that have the greatest therapeutic potential. Oxidative stress has been attributed as one of the important factors in progression of AD (Mubeenand Stephen, 2010). An importance has been given for the use of flavonoids to reduce the oxidative stress in the neurons (Christopher and Sylvain Doré,2011). Curcumin is the principal curcuminoid of the spice turmeric (*Curcuma longa*), a member of the ginger family (Figure 1) (Stagos and Amougias, 2012). Besides having a number of pharmacological properties (Siddique and Ara, 2012), in our earlier study it was reported to inhibit the induction of apoptosis in the AD model flies (Hong and Lee, 2012). In the present study, the effect of curcumin and *Lactococcus lactis* was studied on the life span, oxidative stress, and flight ability in the brains of transgenic *Drosophila* model of AD.

*Lactococcus lactis* (LAL) is an excellent source of dietary antioxidants. The scavenger potential of LAL in oxidative stress (OS) and vascular disease has been described and recent studies in *Drosophila* suggest that microbiota may be beneficial to individuals suffering from neuro degenerative diseases (Maity and Kumar, 2008). Therefore, in this study we describe the protective effects of curcumin and LAL concentrate on a transgenic *Drosophila* model of AD.

## Materials and Methods

### Drosophia Strain

Transgenic fly lines that expressed wild-type human Aβ42 under UAS control in neurons were obtained from Bloomington Drosophila Stock Center (Indiana University, Bloomington, IN). The progeny expressing the human Aβ42 was generated by crossing males of UAS (Upstream Activation Sequence)-Aβ42 strains with the females of GAL4-GMR (Ping and Hahm, 2015). Curcumin is purchased by Sigma-Aldrich (Gillingham, Dorset U.K). gQlab-S is friendly provided by Ildong pharmaceutical. Co. Ltd (Korea).

### Drosophila Culture

The flies were cultured on standard *Drosophila* food containing 0.83% agar, 4.72% corn meal, 4.16% sugar, and 1.67% yeast at 25°C (24 ± 1) (Siddique and Ara, 2012). Crosses were set up as described in earlier published work (Anterand Romero-

Jiménez, 2011). The AD flies were exposed separately to different doses of curcumin (Sigma Aldrich, CAS 458-37-7) or LAL (Ildong pharmaceutical. Co. Ltd, Korea) and mixed in culture medium at final concentration of 25, 50, and 100 $\mu$ Mcurcumin and $2x10^5$, $2x10^6$ and $2x10^7$ LAL. The UAS-Aβ42 acts as a control. The control flies were also separately exposed to the selected doses of curcumin and LAL. Longevity assays in the secondary screen and flies were reared on either 0.25% sucrose or LAL supplemented medium then collected under gaseous $CO_2$ every 24 hours until a minimum of 50 adult females of each genotype were obtained. Briefly, flies were reared on either 0.25% sucrose or $5x10^5$ or $5x10^8$ cell number of LAL with 0.25% sucrose supplemented Tomato Juice medium then collected under gaseous $CO_2$ every 24 hours until a minimum of 50 adult males of each genotype were obtained.

## Lifespan Determination

For the determination of lifespan the newly enclosed female flies (control and AD) were placed in culture tubes (20 flies per tube) containing 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LAL mixed in diet. The flies were transferred to new diet after every 4rd day and the number of dead flies was recorded at 3-day interval until the last one died (Abramoff and Magalhaes, 2004).

## Lipid Peroxidation Assay

Lipid peroxidation test in the brain homogenate was determined according to the method described by Siddique *et al.*, (Anoand Ozawa, 2015). Reagent1 (R1) was prepared by dissolving 64 mg of 1-methyl-2-phenylindole (MEP) into 30 ml of acetonitrile to which 10 ml of methanol was added to bring the volume to 40 ml. The preparation of 37% HCl served as the reagent R2. The brains of flies were isolated under stereo zoom microscope in ice cold Tris-HCl (20 mM) (10 brains/group; five replicates/group). Homogenate was prepared in Tris-HCl and centrifuged at 4500 rpm for 20 min and subsequently the supernatant was collected. In the tube 1300 µl of R1 was taken. A volume of 1µlwas added along with 300µl of R2 vortex and incubated at 45°C for 40 min. After incubation, the tubes were cooled in on ice and centrifuged at 15,000rpm for 10 min at 4°C and read at 586 nm.

## Estimation of Protein Carbonyl Content

The protein carbonyl content was determined according to the method described by Hawkins et al. (Hawkins and Morgan, 2009). The brain homogenate was diluted to a protein concentration of approx. 1 mg/ml. About 250 µl of each diluted homogenate was taken in eppendorf centrifuge tubes separately. To it 250 µl of 10 mM 2,4-dinitrophenyl hydrazine (dissolved in 2.5 M HCl) was added, vortexed, and kept in dark for 20 min. About 125 µl of 50% (w/v) trichloroacetic acid (TCA) was added, mixed thoroughly, and incubated at −20°C for 15 min. The tubes were then centrifuged at 4°C for 10 min at 9,000 rpm. The supernatant was removed and the pellet obtained was washed twice on ice ethanol: ethyl acetate (1:1). Finally, the pellets were redissolved in 1 ml of 6 M guanidine hydrochloride and the absorbance was read at 370 nm.

## Behavioral assays

For the determine of climbing speed, groups of ten 3-day-old females were driven into 18-cm-long vials and incubated for 1 h at room temperature for environmental adaptation. After tapping the flies

completely down to the bottom, we marked their climbing time at the 15-cm finish line when more than five flies had arrived. Five trials were performed for each group and repeated with four different groups. The average climbing time was calculated for each genotype with standard error median value (SEM). Flight assay was performed as previously described (Pesah,2004) with 3-day-old males (n > 50).

## ROS formation measurement

To measure Duox-dependent ROS formation *in vivo*, $H_2O_2$-specific Redox Sensor RedCC-1dye (Molecular probe) was used exactly as described previously (Tanaka and Matsumura,2002). The dissected guts of flies generating ROS sensor were fixed and images plated onto confocal dish for fluorescence analysis under ROI (relative of ratios) using LSM710 Confocal Microscope (Carl Zeiss, Germany)

## Statistical Analysis

Statistical evaluation was used for lifespan expand, lipid peroxidation, estimation of protein carbonyl content, behavioral assay and ROS formation. Mean significant difference between treat groups was determined using one-way analysis of variance (AVOVA). The mean values of protein carbonyl contents, behavior analysis and lipid peroxidation assay of various fly groups were statistically compared using Student's *t*-test. The mean values of represent mean±SE of three experiments

## Results and Discussion

Here, we studied a reduced lifespan in flies when of Aβ42 expression is enhanced in the brain neurons using *Drosophila*model. The survival rate was measured only in female flies. As is evident from Fig. 2, the AD *Drosophila* exposed to 25, 50, and 100 $\mu$M of curcumin showed a dose dependent significant increase in the life span as compared to unexposed AD *Drosophila*. The control flies showed a life span of about 60 days. The median survival time of Aβ42-expressing *Drosophila* was reduced by 30% compared to wild type when both groups were fed a control diet. Interestingly, a diet rich in curcumin partially rescued the reduced lifespan caused by increased neuronal amounts of Aβ42 in *Drosophila* (Fig. 2). Aβ42-expressing *Drosophila* fed a diet containing 100μM of curcumin or 100μM of curcumin and $5x10^7$ LAL had a 20-day (30%) greater median lifespan than those fed a control diet. A concentration of $2x10^5$ LAL dose was slightly observed the survival ratio withAβ42-expressing *Drosophila*. A dose dependent significant delay in the decreased of lifespan was observed in the AD *Drosophila* exposed to 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LAL(Fig. 2). The results obtained for the determination of lifespan are shown in Fig. 1. The AD *Drosophila* exposed to 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LALshowed a dose dependent significant delay in the shorten of lifespan as compared to unexposed AD *Drosophila* and control *Drosophila*.

Viability the number of pupae of filial generation of *Drosophila* exposed to the low dose (25μM) of curcumin was not different (125%) from those in the control group ($P<$ 0.05). The number of pupae of filial generation of *Drosophila* exposed to the high dose 100 μM of curcumin was dramatically lower (51%) than those in control and low dose curcumin group. Meanwhile, the number of pupae of filial generation of *Drosophila* exposed to the low dose ($2x10^5$ of LAL) was not different (113%) from those in the control group

($P$<0.05). The number of pupae of filial generation of *Drosophila* exposed to the high dose $2x10^7$ of LAL was dramatically lower (83%) than those in control and low dose curcumin group. Also, the number of pupae of filial generation of *Drosophila* exposed to the high dose ($2x10^7$ of LAL and100 μM of curcumin) was dramatically lower (46%) than those in control and low dose curcumin group. The data collected for the female flies byfly lifespan was observed by survival ratio (group ($P$<0.005). For control flies the number of survival were more compared to AD flies. Lethality of pupae in group of low concentration 25 μM of curcumin (8%) was slightly lower than in control group (17%). The number of pupae of filial generation of *Drosophila* exposed to the high dose 100 μM of curcumin was slightly lower (16%) than those in control and low dose curcumin group ($P$<0.05). In LAL, *lethality* of pupae in group of low concentration ($2x10^5$) (10%) was slightly lower than in control group (11%). The number of pupae of filial generation of *Drosophila* exposed to the high dose $2x10^7$ of LAL was slightly higher (7%) than those in control and low dose curcumin group ($P$<0.005)(Fig. 3).

No change in the lethality of control flies exposed to 25, 50, and 100 $\mu$M of curcumin was observed (Fig. 3). Lethality of pupae in group of low concentration of 25 $\mu$ Mcurcumin was slightly lower than in control group (Fig. 3). The results obtained for the assay of lipid peroxidation are shown in Fig. 4. The AD flies treated to 25, 50, and 100 $\mu$M of curcumin showed a dose dependent significant decrease in the lipid peroxidation as compared to unexposed AD *Drosophila* and control *Drosophila* (Fig. 4).

Also, the AD *Drosophila* treated to $2x10^5$, $2x10^6$ and $2x10^7$ of LAL showed a dose dependent slight decrease in the lipid peroxidation as compared to unexposed AD *Drosophila* and control *Drosophila* (Fig. 4). The results obtained for the assay of flight ability are shown in Fig.5. The AD *Drosophila* exposed to 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LAL showed a dose dependent significant increase in the flight ability as compared to unexposed AD *Drosophila* and control *Drosophila* (Fig. 5).

Final analysis in this study, the results obtained for protein carbonyl content are shown in Fig. 6. A dose dependent significant decrease in the mean absorbance values was obtained in AD flies exposed to 25, 50, and 100 $\mu$M of curcumin or $2x10^5$, $2x10^6$ and $2x10^7$ of LAL as compared to unexposed AD *Drosophila* and control *Drosophila* (Fig. 6). The unexposed AD *Drosophila* showed the highest mean absorbance value as compared to control *Drosophila*(Fig. 6).

We further analyzed that ROS is abolished in the UAS-Aβ42/GMR-Gal4 flies, indicating that DUOX is required for Aβ42-induced ROS generation and bacteria population. To observe the DUOX activation *in vivo*, we generated transgenic flies that generated ROS by Aβ42 expression, because activated DUOX is known to be localized in the membrane region of the intestine cells. Using these flies, we observed the Aβ42 expression activates ROS formation in gut (Fig. 7 and 8, upper panel right), but the low level of ROS formation observed in curcumin and LAL-treated flies was completely restored to the w118 flies level (Fig. 7 and 8, middle and bottom panel). Importantly, curcumin and LAL were abolished in the UAS-Aβ42/GMR-Gal4 flies, indicating that DUOX is boosted for Aβ42-induced ROS formation. Furthermore, Aβ42-induced ROS formation by curcumin and LAL treatment was abolished in UAS-

Aβ42/GMR-Gal4 flies. These results demonstrated that Aβ42 are boosted for DUOX-expressing intestines but curcumin and LAL is sufficient to retard all of the ROS formation necessary for DUOX-dependent gut immunity that is required for resisting pathogen infection.

## Conclusions

The results of the present study revealed that the exposure of AD *Drosophila* to 25, 50, and 100 $\mu$M of curcumin showed a dose dependent significant increase in the lifespan, reduction in lipid peroxidation, protein carbonyl content, and increase in the flight ability. Oxidative stress as a result of the accumulation of Aβ42 has been reported in neurons of AD *Drosophila* model (Favrin and Bean, 2013). It remains still unclear that the degenerating neuron itself or misfolded proteins directly causes toxicity during the progression of AD (Janet and Helmfors, 2012). In our primary studies with the same *Drosophila* models, various plant extracts and flavonoids have been reported to delay the loss of flight ability and reduced oxidative stress (Jeong and Kim,2014).

**Fig.1** Chemical structure of curcumin.

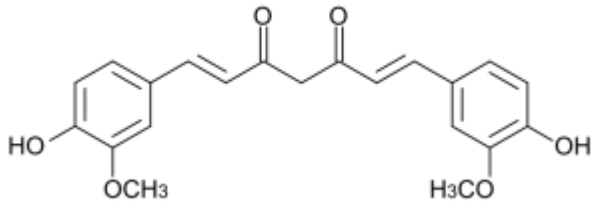



**Fig.2** Effect of curcumin and LAL on survival rate measured in transgenic Drosophilain various treated groups. The concentration indicated with 100 µMcurcumin, 2x107 of LAL.

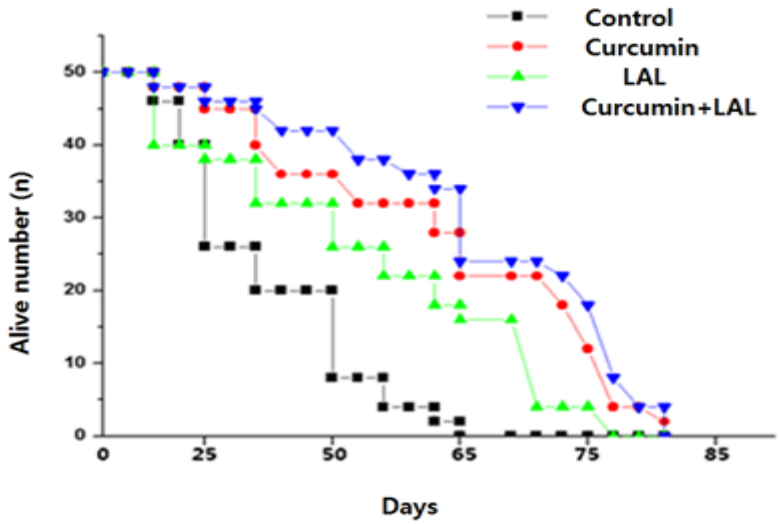


**Fig.3** Curcumin and LAL effect on quantity of pupae in filial generation. Quantity of pupae per vial (three pair of parents). Ten vials per experimental group. Mean ±SEM; *P<0.05: curcumin100 µM vs control and curcumin25 µM and curcumin50 µM. **P<0.01: 2x107 of LALvs control and 2x105 and 2x106 of LAL.

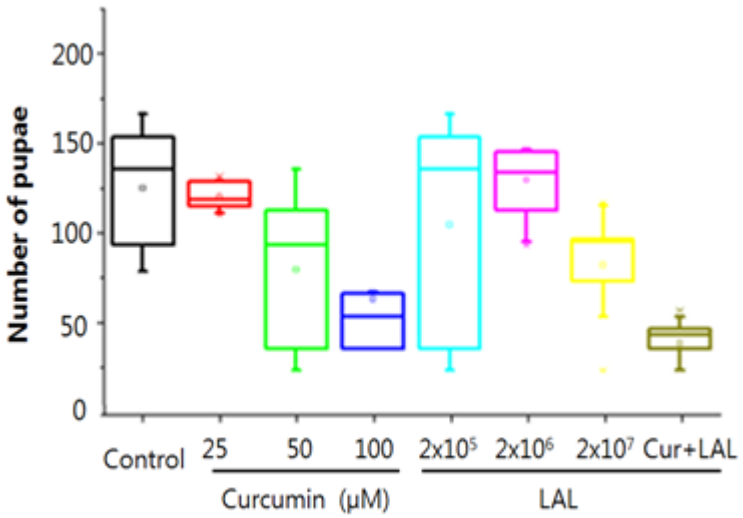
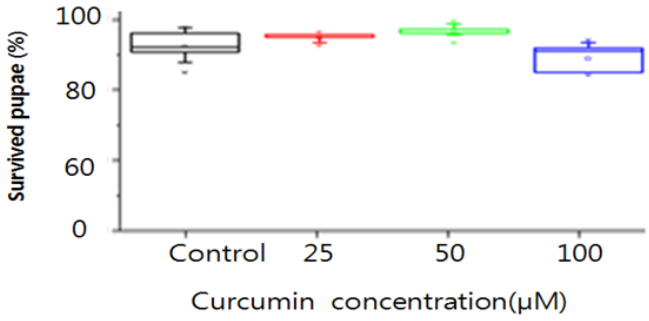
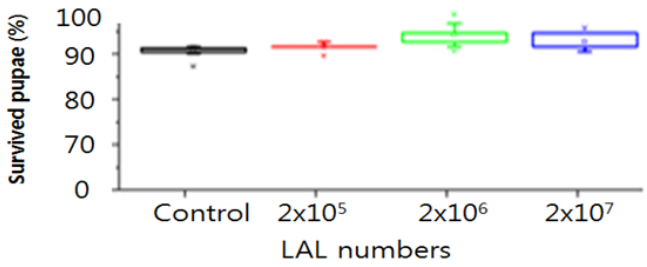



**Fig.4** Curcumin (a) and LAL (b) effect on the lethality of pupae. *P<0.05: curcumin 25 µM vs control, ** P<0.01: curcumin 50 µM vs control and curcumin 100 µM. *P<0.05: LAL 2x105 vs control, **P<0.01: LAL 2x106 vs control and 2x107 LAL




a)




b)

**Fig.5** Curcumin (a) and LAL (b) effect on lipid peroxidation measured in the brains of transgenic Drosophila after 24 days of the exposure in treated groups. (C1=25 µM curcumin; C2=50 µM curcumin; C3=curcumin 100 µM); * Significant with respect to control, P<0.05; **Significant with respect to AD model flies, P<0.01; (C4=2x105 LAL; C5=2x106 LAL; C6=2x107 LAL). # Significant with respect to AD model flies, P<0.005).

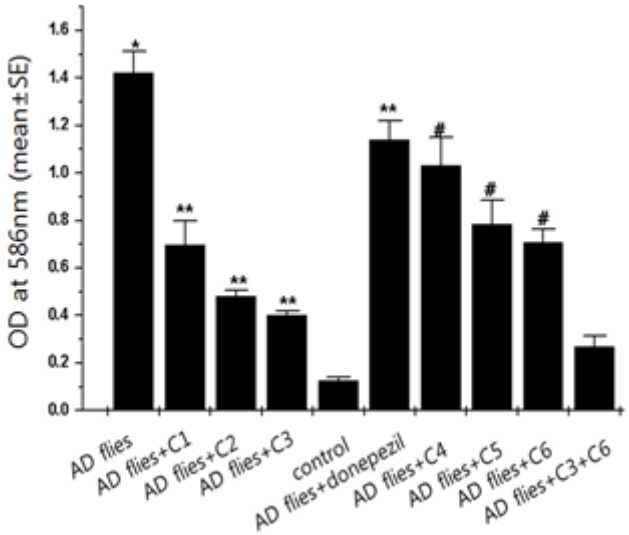



**Fig.6** Curcumin and LAL effect on vertical flight ability. Flight index % of flies moved to the top vial; mean ±SEM; P<0.05: Curcumin vs control group, two ways ANOVA, Bonferroni adjusted.

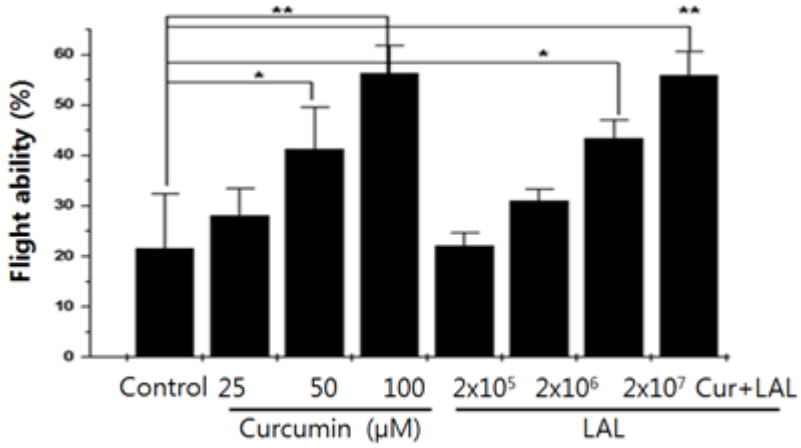


**Fig.7** Effect of curcumin and LAL on protein carbonyl content measured in the brains of transgenic Drosophila after 24 days of the exposure in various treated groups.(25µM, 50µM and 100µM curcumin; a significant with respect to AD model, *P< 0.05; a significant with respect to AD model flies, *P< 0.05).(25µM, 50µM and 100µM curcumin; a significant with respect to control, **P<0.01; significant with respect to AD Drosophila model, **P<0.01). (LAL 2x105; LAL 2x106; LAL 2x107; a significant with respect to AD Drosophila model, P<0.05; significant with respect to AD Drosophila model, P<0.01).# P<0.005, significant with respect to AD Drosophila model, a significant with respect to AD Drosophila model, #P<0.005, donepezil vs AD Drosophila model. Standard control used with 100µg/ml donepezil.

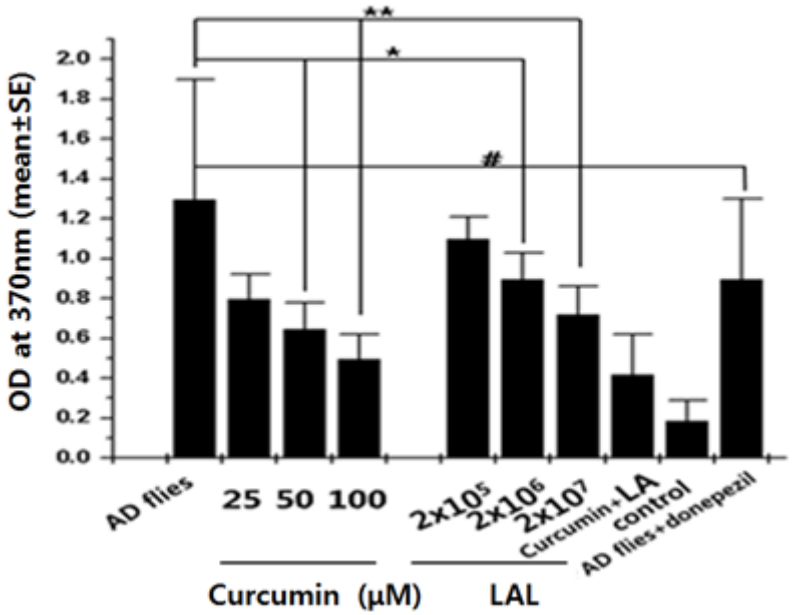
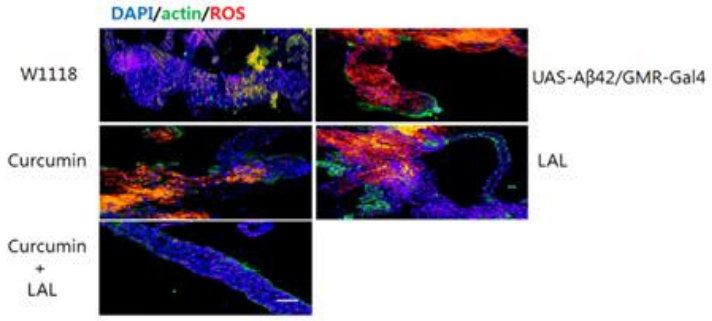
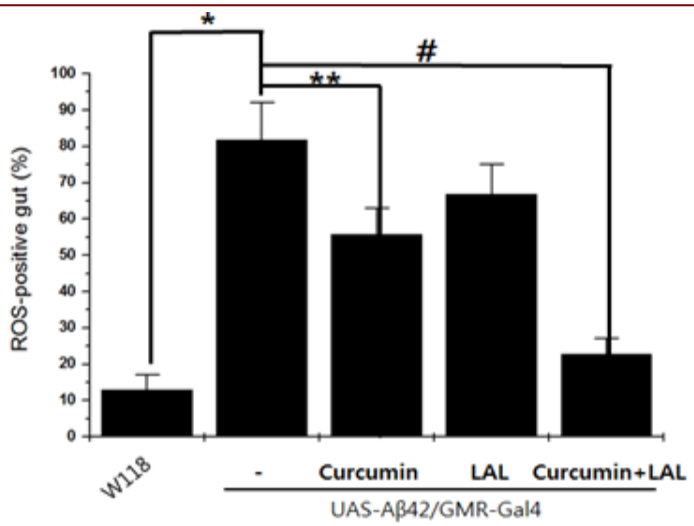



**Fig.8** Curcumin and LAL treatment was repressed with ROS formation in UAS-Aβ/GMR-Gal4 flies. All flies (3days-old) were orally treated with 100µM curcumin or LAL 2x107 for 24h and Duox dependent ROS formation in the midgut was visualized by H2O2-specific RedoxSensor RedCC-1dye (red). Representative Confocal microscopic images (a) and percentage of ROS-positive intestines were shown (b). Data were analyzed using an AVOVA analysis and values represent mean mean±SEM (*P<0.05, **P<0.01, #P<0.005) of at least three independent experiments.




a)




b)

Flavonoids have been reported to show improvements in cognition function possibly by protecting vulnerable neurons or by stimulating neuronal regeneration (Zhang and Ruolph, 2012). In present study, treatment of curcumin has shown reduction in lipid peroxidation and protein carbonyl content in the brains of AD *Drosophila* model. This protection is attributed to an antioxidant nature of curcumin (Caesar and Jonson, 2012). Recent findings have suggested that flavonoids have a remodeling effect on the nature of curcumin, converting them into nontoxic, smaller amorphous aggregates, thus preventing the formation of reactive oxygen species (Rona, 2014). On the other hand, an antioxidant nature of the curcumin is attributed to its unique conjugated structure that includes two methoxylated phenols (Barzegar, 2011). It has been reported to inhibit the generation of ROS responsible for DNA and membrane damage (Grabowska and Kucharewicz, 2015). Although the animals are well acquainted with the self-defense mechanism, an enhancement in stress beyond the capacity of an animal to cope up may result in cellular damage leading to the cell death (Ray and Bisht, 2011). In previous reports, curcumin has shown the neuro-protection in the Aβ42 *Drosophila* model due to its antioxidant potential and its capability to penetrate into the brain (Jeremy and Liu, 2014). It has been reported to alleviate Aβ42-induced toxicity, reduce ROS level, and protect cell against apoptosis (James and Barbara, 2010). The aggregation of Aβ42 in the brain has been implicated as a crucial step in the formation of plaques and curcumin has anti-fibrillogenic and fibril-destabilizing properties, thus inhibiting the formation of Aβ42 fibrillar or plaques (Siddique and Smita, 2014). In *D. melanogaster*, curcumin have been reported to extend life span in a gender and genotype specific manner (Shen and Peng, 2013). In present study, the life span and flight ability were studied on female AD *Drosophila*. There are reports on the life span extension of curcumin in mice and *Caenorhabditi selegans* (Luisa and Stefania, 2013). This extension is due to the neuro-protective, lifespan and lipid peroxidation properties of curcumin (Seongand Lee, 2015). The therapies involving natural antioxidants/ plant products may be used as adjunct therapy. These results obtained in our present study and our primary study, in

which the watermelon and LAL was studied using the same AD fly strain, results in neuro-protective effects (Koand Eun, 2014). The present study was carried out usingAβ42-induced AD *Drosophila* model and consequent flight dysfunction. The this *Drosophila* model mimics the neuronal injury associated with AD and can be used to study whether or not a variety of natural compounds or medicines mixed in the fly feds have the neuroprotective potential.

Thus far, several previous studies have highlighted curcumin and LAL as a main player in regulating AD. For instance, AD inhibits lifespan shorten by regulating curcumin or LAL in a mice model and an AD model (35-39). With this *in vivo Drosophila* model organism, the data presented here add additional evidence supporting curcumin and LAL emerging role as a potentially attractive agent that could prevent AD. Taken together, in this report, the novel effects of curcumin and LAL on regulating lifespan and its capacity to mitigate environmental oxidative stresses and flight ability are described using *Drosophila* as an *in vivo* model organism. Considering that it has become one of most widely administered well-being food supplements in Korea and in western countries, this report would spur further research to discover curcumin and LAL poorly characterized health benefits, thereby eventually helping pave new avenues to utilize curcumin and LAL as a key component in medical regimens in order to prevent and cure many forms of neuronal degeneration.

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